Cardiovascular Effects of Infusions of Epinephrine and Angiotensin Singly and in Combination

By Peter F. Binnion, M.A., B.M., M.Sc. (Med.), and J. Donald Hatcher, M.D., Ph.D.

In hemorrhagic hypotension epinephrine and renin are liberated, and some of the cardiovascular changes noted may be due to the modifying effect of one substance on the action of the other. An increased vascular reactivity to adrenergic drugs has been noted in human and experimental hypertension in which there is evidence of increased levels of angiotensin in the blood. A direct interaction on vessels has been demonstrated by Mylon and Heller who used semipurified angiotensin. This preparation produced no significant effect on the vessels of the isolated rabbit ear, but produced marked vasoconstriction when mixed with subthreshold amounts of epinephrine. Angiotensin infusions produce increased urinary excretion of aldosterone, and increased aldosterone has been noted in hypertensive patients and in hemorrhagic hypotension. Since aldosterone is capable of potentiating the action of adrenergic drugs, it is possible that the increased vascular reactivity to adrenergic drugs noted in the early phase of shock and in hypertensive patients is due to the increased aldosterone level.

In order to determine the extent of the interaction of angiotensin and epinephrine on the cardiovascular system, we have studied the effect of infusion of these two substances singly and in combination.

Methods

All dogs were anesthetized with sodium pentobarbital, the initial dose being 30 mg/kg intravenously followed by doses of 60 to 120 mg intramuscularly every one to two hours as necessary.

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Cardiovascular measurements and calculations listed in the tables were carried out by methods previously described and were begun two to two and one half hours after the initial dose of anesthesia.

The angiotensin preparation used was the *synthetic val angiotensin II-ylpeptide (Ciba prep. 19999a), the powder was dissolved in saline and stored in a refrigerator at 0°C prior to use. Synthetic epinephrine bitartrate (British Drug Houses) was made up with isotonic saline immediately prior to use, and doses were calculated as concentrations of the base. Cardiovascular measurements were made before the infusion was started, after 15 minutes and 30 minutes of infusion, and 15 minutes after the completion of the infusion. Control experiments were done in which isotonic saline was infused.

Skeggs and Kahn gave an infusion of 0.2 Goldblatt units per minute (equivalent to 0.05 meg angiotensin II per minute) to nephrectomized dogs and found a lower blood angiotensin level than that noted in malignant hypertensive dogs. Hence the rates of infusion of angiotensin chosen by us, namely 0.05 and 0.1 meg/kg per min, probably produce blood concentrations close to those expected in certain situations. For epinephrine the rates of infusion were 0.1 or 0.2 meg/kg per min which are in the same range as the rates of secretion considered to occur in certain stressful situations. All solutions were infused at a rate of 0.45 ml/min for 30 minutes through a polyethylene catheter inserted into the jugular vein.

Results

CONTROL INFUSION WITH ISOTONIC SALINE

Eight dogs were infused with isotonic saline; there was no significant change in the cardiovascular parameters measured.

ANGIOTENSIN INFUSION (0.05 MCG/KG PER MIN)

In nine dogs there was a decrease in cardiac output which was of borderline significance.

*Kindly supplied by Ciba Company Limited, Montreal, Quebec.
### TABLE 1A

**Statistical Summary of Infusion Data**

<table>
<thead>
<tr>
<th></th>
<th>O₂ Consumption</th>
<th>A-V O₂ difference</th>
<th>Cardiac output</th>
<th>Stroke volume</th>
<th>Heart rate</th>
<th>Stroke work</th>
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<tr>
<td></td>
<td>10</td>
<td>30</td>
<td>10</td>
<td>30</td>
<td>15</td>
<td>15-30</td>
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<tr>
<td>A. Saline infusion control (n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.8</td>
<td>1.4</td>
<td>0.5</td>
<td>3.6</td>
<td>5.1</td>
<td>12.6</td>
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<tr>
<td>SEM</td>
<td>± 0.4</td>
<td>± 0.5</td>
<td>± 0.5</td>
<td>± 0.4</td>
<td>± 0.5</td>
<td>± 0.5</td>
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<tr>
<td>BPI</td>
<td>&gt; 0.5</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
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</table>

**Mean + 3.6 + 1.0 + 5.1 + 12.6 + 1.5 — 5.7**

**Pi = 0.05**

**SEM ± 8.7 ± 9.5 ±22.6 ±11.1 ±18.2 ± 6.0**

**Pi = 0.15 > 0.5**

**SEM ± 4.3 ± 6.5 ±15.3 ±10.5 ±12.4 ± 4.6**

**Mean — 0.8 — 3.4 — 3.4 — 2.6 — 0.1 — 0.2**

**Pi = 0.03**

**SEM ± 2.1 ± 3.2 ± 4.6 ± 5.9 ± 4.0 ± 2.9**

**Pi = 0.03**

**SEM ± 1.6 ± 2.5 ± 3.8 ± 11.0 ± 12.5 ± 4.0**

**Pi = 0.01**

**SEM ± 0.5 ± 0.2 ± 0.5 ± 0.5 ± 0.2 ± 0.5**

**P ≤ Significance of change as compared with group infused with epinephrine 0.1 mcg/kg per min.**

**P ≤ Significance of change as compared with group infused with angiotensin 0.05 mcg/kg per min.**

**P ≤ Significance of change as compared with control group infused with normal saline.**

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**E. Epinephrine infusion 0.1 mcg/kg per min**

**F. Epinephrine infusion 0.2 mcg/kg per min**

**G. Epinephrine infusion 0.2 mcg/kg per min and angiotensin 0.05 mcg/kg per min**

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**Note:**

- Statistical abbreviations: Mean = Mean, SEM = Standard Error of the Mean, SD = Standard Deviation, Pi = Significance of change as compared with control group infused with normal saline.
- B = Significance of change as compared with group infused with epinephrine 0.1 mcg/kg per min.
- Pi = Significance of change as compared with group infused with angiotensin 0.05 mcg/kg per min.
- P ≤ Significance of change as compared with group infused with epinephrine 0.2 mcg/kg per min.

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**References:**


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**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>A. Saline infusion control (n = 8)</th>
<th>B. Epinephrine infusion 0.1 mcg/kg per min (n = 8)</th>
<th>C. Angiotensin infusion 0.05 mcg/kg per min (n = 9)</th>
<th>D. Infusion of epinephrine 0.1 mcg/kg per min and angiotensin 0.05 mcg/kg per min (n = 9)</th>
<th>E. Epinephrine infusion 0.2 mcg/kg per min (n = 10)</th>
<th>F. Infusion of epinephrine 0.2 mcg/kg per min and angiotensin 0.05 mcg/kg per min (n = 9)</th>
<th>G. Infusion of epinephrine 0.2 mcg/kg per min and angiotensin 0.1 mcg/kg per min (n = 7)</th>
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<td></td>
<td>Total peripheral resistance</td>
<td>Arterial pressure</td>
<td>Change in right ventricular pressure</td>
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<td>Baseline</td>
<td>Change</td>
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<td>±1.5 ± 1.5</td>
<td>±1.6 ± 1.6</td>
<td>±1.5 ± 1.5</td>
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</tbody>
</table>

P<0.05 = Significance of change as compared with control group infused with normal saline.
P<0.01 = Significance of change as compared with group infused with epinephrine 0.1 mcg/kg per min.
P<0.05 = Significance of change as compared with group infused with angiotensin 0.05 mcg/kg per min.
P<0.01 = Significance of change as compared with group infused with epinephrine 0.2 mcg/kg per min.
after 15 minutes of infusion although highly significant after 30 minutes of infusion. There was a slight decrease in heart rate and stroke volume, but neither change was statistically significant when compared to the group infused with saline. Arterial diastolic blood pressure rose more than systolic blood pressure, and the calculated total peripheral resistance was increased. Oxygen consumption was increased after 30 minutes of infusion. Fifteen minutes after stopping the angiotensin infusion all cardiovascular parameters were within normal limits.

**EPINEPHRINE INFUSION (0.1 MCG/KG PER MIN)**

In this group of eight dogs there were no significant changes noted.

**EPINEPHRINE INFUSION (0.2 MCG/KG PER MIN)**

After 15 minutes of infusion in these ten dogs, there was a marked rise in cardiac output associated with an increase in oxygen consumption and a decrease in arteriovenous oxygen difference. The rise in cardiac output was the result of an increase in stroke volume, without significant elevation of heart rate. Arterial diastolic pressure fell, while right ventricular systolic pressure rose. There was an increase in left ventricular systolic work despite a fall in total peripheral resistance. After 30 minutes of epinephrine infusion, qualitatively similar results were obtained, although in some instances they were less marked. Fifteen minutes after the infusion was stopped oxygen consumption was still increased.

**INFUSION OF ANGIOTENSIN (0.05 MCG/KG PER MIN) IN COMBINATION WITH EPINEPHRINE (0.1 MCG/KG PER MIN)**

In these nine dogs, the significance of results was determined by comparison with the changes noted on infusion of saline (p1 values), of epinephrine alone (p2 values) and of angiotensin alone (p3 values) at these doses (table 1A and B).

With the combination of drugs arterial pressure was increased throughout the infusion at levels comparable to those seen with angiotensin alone. After 15 minutes of infusion the combination produced an increase in cardiac output, stroke volume and left ventricular stroke work whereas epinephrine and angiotensin alone did not have these effects. The increase in these parameters with the combination was significantly different from those seen with angiotensin alone, but only the increase in stroke work was statistically different from that noted with epinephrine alone. This apparent augmentation was not sustained throughout the 30 minutes of infusion (table 1A and B). Fifteen minutes after stopping the infusion there was no change in any cardiovascular parameter.

**INFUSION OF EPINEPHRINE (0.2 MCG/KG PER MIN) IN COMBINATION WITH ANGIOTENSIN (0.05 MCG/KG PER MIN OR 0.1 MCG/KG PER MIN)**

With two exceptions, the addition of angiotensin at either level to this dose of epinephrine did not alter the responses seen with epinephrine alone. Examination of the data in table 1B indicates that epinephrine combined with the smaller dose of angiotensin produced changes in arterial pressure which are, in general, what one would expect if the effects of these drugs alone were summated. Although the combination of epinephrine with the smaller dose of angiotensin increased left ventricular stroke work above that seen with epinephrine alone, this increase was not statistically significant. This increase was significant when epinephrine was combined with the larger dose of angiotensin. In both dose combinations, the increase in stroke work was less marked after 30 minutes of infusion. The increase in stroke work cannot be explained by the effect of this dose of angiotensin alone on this parameter, for doses of angiotensin 4 to 10 times greater than those employed do not increase left ventricular stroke work.

**Discussion**

The cardiovascular responses to angiotensin infusion in anesthetized dogs have been reported by other investigators, and we confirm that it appears to be essentially a peripheral vasoconstrictor. There is no evidence of an inotropic cardiac effect.
With regard to epinephrine, no significant cardiovascular changes occurred when it was infused at a dose of 0.1 meg/kg per min, although marked changes occurred when the rate of infusion was doubled. Our findings with regard to the larger dose are in agreement with previous observations.17, 18

The apparent augmentation of effect on cardiac output and left ventricular stroke work observed when epinephrine and angiotensin in small doses are combined, and on stroke work when larger doses are combined, is an interesting observation. This augmentation is not shared by the other cardiovascular parameters measured.

There is evidence for a possible interaction between angiotensin and epinephrine with respect to vasoconstrictor activity.4 In experiments in this laboratory on the isolated heart infused with these drugs alone and in combination, no evidence was obtained to suggest that the apparent augmentation of effect seen in intact animals on cardiac output and stroke work was due to direct myocardial action.19 It may be that this augmentation in the intact animal occurs by an indirect mechanism, possibly by stimulation of the adrenal cortex. Angiotensin causes the release of aldosterone and small amounts of other steroids.5 Nasmyth21 has tested the effects of corticosteroids alone and in association with epinephrine on the isolated mammalian heart, and no increase in the cardiac activity of epinephrine was detected; potentiation has been noted in elasmobranchs.22 The cardiac output elevation due to norepinephrine is not changed by hydrocortisone or aldosterone23 although some steroids alone do exert a positive inotropic effect on the hypodynamic cat papillary muscle24 and on the heart lung preparation from adrenalectomized rats.23 The augmentation of effect on cardiac output and stroke work noted with combinations of angiotensin and epinephrine may involve the release of aldosterone and the interaction of all three substances, but there is no conclusive evidence to support this contention. The interaction of these three substances on cardiovascular function may be of importance in shock and hypertension.1-3, 10

The transient nature of this augmentation of action on cardiac output and stroke work produced by combinations of angiotensin and epinephrine suggests that this interaction is not of long-term importance in cardiovascular adjustments to certain stressful situations in which these two hormones are present in increased amounts. It may be of importance in the initial response in certain types of acute stress.

**Summary**

Angiotensin infused at 0.05 meg/kg per min for 30 minutes into anesthetized dogs reduces cardiac output, raises arterial blood pressure, increases total peripheral resistance, but does not raise right ventricular pressure nor change left ventricular stroke work. It is suggested that this infusion rate may be comparable to the rate of production under certain conditions.

The cardiovascular action of epinephrine given at rates similar to those occurring under stress, namely 0.1 meg/kg per min and 0.2 meg/kg per min for 30 minutes, are discussed. In the former dose no cardiovascular effects are seen, but with the latter dose the usual cardiovascular effects were observed.

A transient augmentation of effect on cardiac output and stroke work is noted with a combination of epinephrine 0.1 meg/kg per min and angiotensin 0.05 meg/kg per min, and of stroke work alone when the dose of each is doubled. It is suggested that the physiological importance of this interaction may be limited to the initial phases of certain stresses in which both these substances are released. The mechanism of this effect is not clear, but may be the result of the interaction of epinephrine, angiotensin and aldosterone.

**Acknowledgment**

The authors acknowledge the technical assistance of Mrs. M. Dean, Mrs. U. Connal, and Mrs. S. Holt.

**References**

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